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- b) ~~contacting said substance with the opioid receptor polypeptide; and~~
- c) ~~detecting the ability of the substance to specifically bind to the opioid receptor polypeptide.~~

REMARKS


Applicants provide this amendment to supplement the Second Submission for the purpose of correcting amendments made in the Second Submission pertaining the sequence of the second extracellular loop. In the Second Submission, Applicants responded to the rejection of claims 103-114 and 129-135 under 35 U.S.C. §112, first paragraph, for nonenablement by indicating claims were being amended to recite the amino acid sequence for the second extracellular loop. However, by error, claims were amended to recite SEQ ID NO:17, which is not the amino acid sequence for the second extracellular loop, but for the second intracellular loop. Specification at page 96, lines 1-8. This paper corrects this error. These amendments are supported in the specification as described below.

In FIG. 1, the seven transmembrane domains of the protein are indicated as TM1-TM7. Specification at page 24, lines 2-3 (Brief Description for FIG. 1). The amino acid sequence for the second extracellular loop, Specification at page 96, lines 7-8, identifies it as the region in FIG. 1 between TM3 and TM4; the amino acid sequence for the third extracellular loop, Specification at page 93, line 31 to page 94, line 6, identifies it as the region in FIG. 1 between TM5 and TM6. A person of ordinary skill in the art knows that intracellular loops alternate with extracellular loops between transmembrane domains. Consequently, that person knows that the second extracellular loop is between TM4 and TM5 because the first extracellular loop is between TM2 and TM3 and the first intracellular loop is between TM1 and TM2 (the region before the first transmembrane domain is not a loop because only one side crosses the

transmembrane). Thus, the amino acid sequence for the second extracellular loop of a mouse kappa opioid receptor polypeptide is disclosed in the Specification in FIG. 1 as GGTKVREDVDVIECSLQFPDDEYSWW in SEQ ID NO:2. The comparison between the mouse and human kappa opioid receptors shown in FIG. 4a indicates that the sequence of the second extracellular loop of the human kappa opioid receptor polypeptide is GGTKVREDVDVIECCLQFPDDDYWW.

Applicants believe these amendments, in conjunction with the Second Submission, place the claims in condition for allowance. Should the examiner have any questions or comments, a telephone conference is earnestly solicited to discuss such matters.

Respectfully submitted,



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APPENDIX A:**Claims with Amendments Shown**

103. (Amended three times) A process of isolating a substance with an ability to act as a specific agonist of a kappa opioid receptor, said process comprising the steps of:

- a) providing an opioid receptor polypeptide comprising [SEQ ID NO:17] a second extracellular comprising the amino acid sequence GGTKVREDVDVIECSLQFPDDEYSWW, wherein the polypeptide is encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:1;
- b) contacting said opioid receptor polypeptide with a composition comprising said substance;
- c) detecting the ability of said substance to act as a specific agonist of said opioid receptor; and
- d) isolating said substance if the ability of said substance to act as a specific agonist of the opioid receptor is detected.

109. (Amended three times) A process of isolating a substance with an ability to act as a specific agonist of a kappa opioid receptor, said process comprising the steps of:

- a) providing an opioid receptor polypeptide comprising the second extracellular loop comprising the amino acid sequence GGTKVREDVDVIECCCLQFPDDDYSSWW[SEQ ID NO:17] and encoded for by a nucleic acid sequence comprising at least 60 contiguous bases of SEQ ID NO:11;
- b) contacting said opioid receptor polypeptide with a composition comprising said substance;

- c) detecting the ability of said substance to bind to said opioid receptor polypeptide; and
- d) isolating said substance if the ability of said substance to specifically bind to the opioid receptor polypeptide is detected.

117. (Amended twice) The process of claim 116, wherein the chimeric opioid receptor polypeptide comprises a second extracellular loop comprising the amino acid sequence GGTKVREDVDVIECSLOFPDDEYSWW[SEQ ID NO:17].

129. (Amended three times) A process of screening a substance for its ability to act as a specific agonist of a kappa opioid receptor comprising:

- a) expressing a chimeric recombinant opioid receptor polypeptide comprising a second extracellular loop comprising the amino acid sequence GGTKVREDVDVIECSLOFPDDEYSWW[SEQ ID NO:17], wherein said opioid receptor polypeptide is encoded by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:1;
- b) contacting said substance with the opioid receptor polypeptide; and
- c) detecting the ability of the substance to specifically bind to the opioid receptor polypeptide.

137. (Amended) A process of screening a substance for its ability to act as a specific agonist of a kappa opioid receptor comprising:

- a) expressing a chimeric recombinant opioid receptor polypeptide comprising the second extracellular loop comprising the amino acid sequence GGTKVREDVDVIECCLOFPDDDDYSWW[SEQ ID NO:17], wherein said chimeric opioid receptor polypeptide is encoded by a nucleic acid sequence comprising 60 contiguous bases of SEQ ID NO:11;

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- b) contacting said substance with the opioid receptor polypeptide; and
- c) detecting the ability of the substance to specifically bind to the opioid receptor polypeptide.

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APPENDIX B:**Pending Claims**

91. A process of screening a substance for its ability to specifically bind to an opioid receptor, said process comprising the steps of:

- a) expressing a recombinant opioid receptor polypeptide encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:1;
- b) contacting said substance with the opioid receptor polypeptide; and
- c) detecting the ability of said substance to specifically bind to said opioid receptor polypeptide.

92. The process of claim 91, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 40 contiguous bases of SEQ ID NO:1.

93. The process of claim 92, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 50 contiguous bases of SEQ ID NO:1.

94. The process of claim 93, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 75 contiguous bases of SEQ ID NO:1.

95. The process of claim 94, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 100 contiguous bases of SEQ ID NO:1.

96. The process of claim 95, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 680 contiguous bases of SEQ ID NO:1.

97. A process of screening a substance for its ability to specifically bind to an opioid receptor, said process comprising the steps of:

- a) expressing a recombinant opioid receptor polypeptide encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:11;
- b) contacting said substance with the opioid receptor polypeptide; and
- c) detecting the ability of said substance to specifically bind to said opioid receptor polypeptide.

98. The process of claim 97, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 40 contiguous bases of SEQ ID NO:11.

99. The process of claim 98, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 50 contiguous bases of SEQ ID NO:11.

100. The process of claim 99, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 75 contiguous bases of SEQ ID NO:11.

101. The process of claim 100, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 100 contiguous bases of SEQ ID NO:11.

102. The process of claim 101, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 680 contiguous bases of SEQ ID NO:11.

103. A process of isolating a substance with an ability to act as a specific agonist of a kappa opioid receptor, said process comprising the steps of:

- a) providing an opioid receptor polypeptide comprising a second extracellular comprising the amino acid sequence GGTKVREDVDVIECSLQFPDDEYSWW, wherein the polypeptide is encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:1;

- b) contacting said opioid receptor polypeptide with a composition comprising said substance;
- c) detecting the ability of said substance to act as a specific agonist of said opioid receptor; and
- d) isolating said substance if the ability of said substance to act as a specific agonist of the opioid receptor is detected.

104. The process of claim 103, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 40 contiguous bases of SEQ ID NO:1.

105. The process of claim 104, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 50 contiguous bases of SEQ ID NO:1.

106. The process of claim 105, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 75 contiguous bases of SEQ ID NO:1.

107. The process of claim 106, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 100 contiguous bases of SEQ ID NO:1.

108. The process of claim 107, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 680 contiguous bases of SEQ ID NO:1.

109. A process of isolating a substance with an ability to act as a specific agonist of a kappa opioid receptor, said process comprising the steps of:

- a) providing an opioid receptor polypeptide comprising the second extracellular loop comprising the amino acid sequence GGTKVREDVDVIECCLQFPDDDDYSWW and encoded for by a nucleic acid sequence comprising at least 60 contiguous bases of SEQ ID NO:11;

- b) contacting said opioid receptor polypeptide with a composition comprising said substance;
- c) detecting the ability of said substance to bind to said opioid receptor polypeptide; and
- d) isolating said substance if the ability of said substance to specifically bind to the opioid receptor polypeptide is detected.

112. The process of claim 109, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 75 contiguous bases of SEQ ID NO:11.

113. The process of claim 112, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 100 contiguous bases of SEQ ID NO:11.

114. The process of claim 113, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 680 contiguous bases of SEQ ID NO:11.

116. The process according to claim 91, wherein said opioid receptor polypeptide is a chimeric opioid receptor polypeptide.

117. The process of claim 116, wherein the chimeric opioid receptor polypeptide comprises a second extracellular loop comprising the amino acid sequence GGTKVREDVDVIECSLQFPDDEYSWW.

118. The process of claim 116, wherein the chimeric opioid receptor polypeptide comprises SEQ ID NO:14.

119. The process of claim 116, wherein the chimeric opioid receptor polypeptide comprises polypeptide portions of both kappa and delta opioid receptors.

120. The process according to claim 116, wherein the chimeric opioid receptor polypeptide comprises $\kappa_{1-78}/\delta_{70-372}$ or $\delta_{1-69}/\kappa_{79-380}$.

121. The process according to claim 91, wherein the opioid receptor polypeptide is a kappa opioid receptor polypeptide having the sequence of SEQ ID NO:2.

122. The process of claim 121, wherein said opioid receptor polypeptide is a kappa opioid receptor polypeptide encoded for by the polynucleotide of SEQ ID NO: 1.

123. The process of claim 143, wherein said opioid receptor polypeptide is a kappa opioid receptor polypeptide encoded for by the polynucleotide of SEQ ID NO: 11.

125. The process of claim 103, wherein the opioid receptor polypeptide is a chimeric opioid receptor polypeptide.

126. The process of claim 125, wherein one polypeptide of the chimeric opioid receptor polypeptide comprises the third extracellular loop of delta opioid receptor.

127. The process of claim 125, wherein the opioid receptor polypeptide comprises portions of both kappa and delta opioid receptors.

128. The process of claim 125, wherein the chimeric polypeptide comprises $\kappa_{1-78}/\delta_{70-372}$ or $\delta_{1-69}/\kappa_{79-380}$.

129. A process of screening a substance for its ability to act as a specific agonist of a kappa opioid receptor comprising:

- a) expressing a chimeric recombinant opioid receptor polypeptide comprising a second extracellular loop comprising the amino acid

sequence GGTKVREDVDVIECSLQFPDDEYSWW, wherein said opioid receptor polypeptide is encoded by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:1;

- b) contacting said substance with the opioid receptor polypeptide; and
- c) detecting the ability of the substance to specifically bind to the opioid receptor polypeptide.

130. The process of claim 129, wherein said nucleic acid sequence comprises at least 40 contiguous bases of SEQ ID NO:1.

131. The process of claim 129, wherein said nucleic acid sequence comprises at least 55 contiguous bases of SEQ ID NO:1.

132. The process of claim 129, wherein said nucleic acid sequence comprises at least 70 contiguous bases of SEQ ID NO:1.

134. The process of claim 129, wherein one polypeptide of the chimeric opioid receptor polypeptide comprises the third extracellular loop of kappa opioid receptor.

135. The process of claim 129, wherein the chimeric opioid receptor polypeptide comprises polypeptide portions of both kappa and delta opioid receptors.

137. A process of screening a substance for its ability to act as a specific agonist of a kappa opioid receptor comprising:

- a) expressing a chimeric recombinant opioid receptor polypeptide comprising the second extracellular loop comprising the amino acid sequence GGTKVREDVDVIECCLQFPDDYSWW, wherein said chimeric opioid receptor polypeptide is encoded by a nucleic acid sequence comprising 60 contiguous bases of SEQ ID NO:11;

- b) contacting said substance with the opioid receptor polypeptide; and
- c) detecting the ability of the substance to specifically bind to the opioid receptor polypeptide.

138. The process of claim 137, wherein said nucleic acid sequence comprises 40 contiguous bases of SEQ ID NO:1.

139. The process of claim 137, wherein said nucleic acid sequence comprises 55 contiguous bases of SEQ ID NO:1.

140. The process of claim 137, wherein said nucleic acid sequence comprises 70 contiguous bases of SEQ ID NO:1.

141. The process of claim 137, wherein a portion of the chimeric opioid receptor polypeptide comprises SEQ ID NO:14.

142. The process of claim 137, wherein the chimeric opioid receptor polypeptide comprises polypeptide portions of both kappa and delta opioid receptors.

143. The process according to claim 97 wherein the opioid receptor polypeptide is a kappa opioid receptor polypeptide comprising SEQ ID NO:12.